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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/774,843	02/09/2004	Tony Peled	24024-505	9770
36623 7590 03/18/2008 MINTZ, LEVIN, COHN, FERRIS, GLOVSKY AND POPEO, P.C. ONE FINANCIAL CENTER BOSTON, MA 02111				
EXAMINER LEAVITT, MARIA GOMEZ				
ART UNIT		PAPER NUMBER		
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary

Application No.

10/774,843

Applicant(s)

PELED ET AL.

Examiner

MARIA LEAVITT

Art Unit

1633

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 30 October 2007.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 401, 411, 412, 414, 416-419, 422-424, 437, 438 and 462-468 is/are pending in the application.
- 4a) Of the above claim(s) 463 and 468 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 401, 411, 412, 414, 416-419, 422-424, 437, 438, 462 and 464-467 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-946)
- 3) ☐ Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date _____
- 4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date _____
- 5) ☐ Notice of Informal Patent Application
- 6) ☐ Other: _____

Detailed Action

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 10-30-2007 has been entered.

1. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.
2. The examiner acknowledges receiving the Declaration under 37 C.F.R. § 1.132 signed by Dr. Toni Peled.
3. Claims 401, 411, 412, 414, 416-419, 422-424, 437, 438 and 462-468 are pending; claims 401, 411, 412, 419, 422, 423, 437, 438, 462, 463 have been amended and claims 464-468 have been added by Applicants' amendment filed on 10-30-2007.

Claim Objections

Notice of Non-Compliant Amendment (37 CFR 1.121)

4. The amendment to the claims filed on 10-30-2007 does not comply with the requirements of 37 CFR 1.121(c) because claim 463 has the status identifier of "Currently amended". However, claim 463 is withdrawn from prosecution since it corresponds to non elected subject matter e.g., Group V, in Applicants' response to the restriction requirements by Applicants filed on 11-14-2006. Therefore claims 463 and dependent 468 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected

invention, there being no allowable generic or linking claim. The election was made **without** traverse in the reply filed on 11-14-2006. Applicants' election of Group 1 in Applicants' reply filed on 11-14-2006 was acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)). To be fully responsible to the current office action, amendments to the claims filed on or after 10-30-2007 must comply with 37 CFR 1.121(c) or they will not be entered.

5. Therefore, claims 401, 411, 412, 414, 416-419, 422-424, 437, 438 and 462, 464-467 are currently under examination to which the following grounds of rejection are applicable.

Withdrawn Rejections in response to Applicant arguments or amendments.

Claim Rejections - 35 USC § 112 – first paragraph-enablement

In view of Applicants remarks, in light of the guidance provided in the specification and knowledge available to one of ordinary skill in the art at the time of filing the present application and further in view of Applicants' amendment of claim 401 to recite the hematopoietic stem cells population of CD34+, and the recitation of "about 1.0mM to about 10 mM of exogenously added nicotinamide", rejection of claims 401, 411, 412, 414, 416-419, 422-424, 437, 438 and 462 under - 35 USC § 112 – first paragraph-enablement, has been withdrawn.

Claim Rejections - 35 USC § 112- First paragraph- New Matter

In view of Applicants amendment of claims 401, 411, 412, 462 to recite "about 1.0mM to about 10 mM", rejection of claims 401, 411, 412, 414, 416, 419, 422-424, 437, 438, and 462 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description

requirement has been withdrawn.

Double Patenting

Provisional Rejection, Obviousness Type Double Patenting-No secondary Reference(s)

In view of Applicants' cancellation of claim 208 of copending Application No.

10/767,064, provisional rejection of claim 411 on the ground of nonstatutory double patenting over claim 208 of copending Application No. 10/767,064 is moot.

Rejections maintained in response to Applicant arguments or amendments.

Claim Rejections - 35 USC § 103

Claims 401, 411, 412, 414, 416-419, 422-424, 437-438 and 462 remain rejected and new claims 464-467 are rejected under 35 U.S.C. 103(a) as being unpatentable over Brown R (US Publication No. 2002/0159984, Date of Publication October 31, 2002).

Response to Applicants' Arguments as they apply to rejection of claim 401, 412, 414, 416-419, 422-424, 437-438 and 462 464-467 under 35 USC § 103

On page 9 of Remarks, Applicants argue that Brown does not teach or suggest the limitation "...about 1.0 to about 10 mM nicotinamide..." as required by independent amended claims 401, 411, 412 and 462 as amended herein. Moreover Applicants contend that "this critical feature is not taught or suggested by Brown. Brown merely teaches that nicotinamide is one of a number of "...various vitamins and co-factors, such as riboflavin, nicotinamide, folic acid, choline, biotin, and the like that may be required to sustain cell growth." See, Brown at ¶ [0040]. Brown does not teach or suggest that nicotinamide is an essential component of the medium, and

further Brown does teach or suggest that the addition of nicotinamide in concentrations greater than the 4mg/liter cited in Table 1, is used for the inhibition of differentiation of hematopoietic stem cells". Such is not persuasive.

As an initial matter, the examiner disagrees with Applicants' position that nicotinamide is an essential component as the instant claims broadly embrace a method of expanding a population of CD34+ hematopoietic stem cells *ex-vivo* comprising culturing said cells in a medium comprising nutrients, a combination of cytokines selected from stem cell factor, thrombopoietin (TPO), FLT3, IL-6, and IL-3, in the presence of nicotinamide. Hence nicotinamide is one of the medium components. As stated in the previous office action, Brown R. teaches a method for *ex vivo* expansion (e.g. proliferation) of CD34+/CD38- cells derived from cord blood (p. 1, [0010]) in culture media comprising stem cell factor, TPO, FLT3, IL-6, and IL-3. Additionally Brown R. exemplifies cultures of the bone marrow CD34+ enriched population with significant expansion at various time points including days 3, 7 and 14 (p. 2, [0019]-[0022]). Indeed, Brown teaches that blood cells, can be cultured for as long as 8 weeks to increase the total number of CD34+/CD38- cells obtained (p. 6, [0072]). Moreover, Brown discloses that the culture medium e.g., Iscove's modified Dulbecco's medium (IMDM), comprises nicotinamide at concentration of 4 mg/L (e.g., 0.033mM). Further, Brown discloses that IMDM can reformulated and "it is expected that the reformulation will contain those essential components of IMDM in amounts 0.1 to 10, preferably 0.5 to 2 times, most preferably 0.8 to 1.2 times their amounts" (p. 4, [0045]). Although Brown R. does not explicitly teaches nicotinamide at concentrations of 1.0 mM to 10mM, Brown R clearly recognizes that the concentration of essential components of the IMDM including nicotinamide for expansion of

Comment [a1]: Is the nicotinamide naturally present in IMDM or did Brown add it? Your motivation to modify the components in IMDM, but it is not clear in your rejection that nicotinamide is naturally part of this commercial medium.

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CD34+/CD38- cells *ex vivo* is a result effective variable depending on the desired use, e.g., maintenance, proliferation and/or differentiation of CD34+ . At the time the invention was made it would have been obvious to optimize the ranges of concentration of this result effective variable, therefore the claimed invention would have been obvious.

New Grounds of Rejection

Claim Rejections - 35 USC § 102(b)

The present invention is drawn to a transplantable hematopoietic cell preparation comprising and expanded population of CD34+ hematopoietic stem cells.

The following is a quotation of the appropriated paragraphs of 35 U.S.C. 102 that forms the basis for the rejections under this section made in this Office action:

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claim 412 is rejected under 435 U.S.C. 102(b) as being anticipated Brown et al., (US Patent Number 5,945,337, Date of Patent Aug. 31, 1999).

Brown teaches the expansion of a population of early progenitor stem cells which can be mixed with fresh unfractionated bone marrow which contain CD34+ (col. 6, lines 37-40). Moreover, Brown discloses that the mixed human bone marrow stem cell populations which contain CD34+ cells can be selectively enriched *ex-vivo* to increase the proportion of CD34+ in the population for human therapy (col. 7, lines 15-20).

Thus by teaching all the claims limitations, Brown et al., anticipate the instant invention.

Claim Rejections - 35 USC § 112 (second paragraph)

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 414 and 422 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite in that it fails to point out what is included or excluded by the claim language.

Claim 414 which depends on claim 401 recites "selected from the group consisting of: embryonic stem cell and adult stem cells". However, claim 401 only refers to a "population of CD34+ hematopoietic stem cells". Thus there is not a proper antecedent bases for said embryonic stem cell and adult stem cells as recited in claim 414. As such, the metes and bounds of the claims cannot be determined.

Claim 422 which depends on claim 401 recites "said early acting cytokines". However, claim 401 only refers to a "a combination of cytokines". Thus there is not a proper antecedent bases for said early acting cytokines as recited in claim 422. As such, the metes and bounds of the claims cannot be determined.

Conclusion

Claims 401, 411, 412, 414, 416-419, 422-424, 437, 438, 462 and 464-467 are rejected.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maria Leavitt whose telephone number is 571-272-1085. The examiner can normally be reached on M-F.

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If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach, Ph.D can be reached on (571) 272-0739. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1633; Central Fax No. (571) 273-8300. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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Maria Leavitt, PhD
Patent Examiner P/1633
Remsen 2B55
Phone: 571-272-1085

/Anne Marie S. Wehbe/
Primary Examiner, A.U. 1633